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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,848	07/03/2007	Roberto Pellicciari	35147-503N01US	3802

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
BADIO, BARBARA P	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,848	PELLICCIARI, ROBERTO	
	Examiner	Art Unit	
	Barbara P. Badio	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

First Office Action on the Merits of a RCE

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 13, 2009 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Application

3. Claims 1-3, 5 and 12-18 are pending in the present application. The instant claims are rejected as indicated below.

Double Patenting

4. The rejection of claims 1-3, 5 and 12-18 on the ground of nonstatutory obviousness-type double patenting over claims of US Patent No. 7,138,390 is withdrawn.

The terminal disclaimer filed July 13, 2009 is noted.

5. The provisional rejections of claims 1-3, 5 and 12-18 on the ground of nonstatutory obviousness-type double patenting over claims of copending Application Nos. (a) 11/081,002, (b) 11/602,307 and (c) 11/914,559 are maintained.

Applicant's statement that the filing of a terminal disclaimer will be considered upon notice of allowable subject matter is noted.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3, 5 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutically acceptable salt or amino acid conjugate of a compound of formula (I), does not reasonably provide enablement for a solvate of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in making an enablement rejection are summarized as:

a) the quantity of experimentation necessary,

b) the amount of direction or guidance presented,

c) the presence or absence of working examples,

d) the nature of the invention,

e) the state of the prior art,

f) the relative skill of those in the art,

g) the predictability or unpredictability of the art, and

h) the breadth of the claims.

In re Colianni, 195 USPQ 150 (CCPA 1977). *In re Rainer*, et al., 146 USPQ 218 (CCPA 1965). *Ex parte Formal*, 230 USPQ 546 (BPAI 1986).

a) Determining if a particular compound would form a solvate or hydrate would require synthesis and recrystallization of the compound solvate or hydrate using a variety of solvents, temperatures and humidities. The experimentation for solvates or hydrates is potentially open-ended.

b) The specification merely mentions the Applicant's intention to make solvates and hydrates, without teaching the preparation thereof.

c) While the claims recite solvates and hydrates, no working examples show their formation. As stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed.Cir. 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The specification shows no evidence of the formation and actual existence of solvates and hydrates. Hence, Applicant must show formation of solvates and hydrates or limit the claims accordingly.

d) The nature of the invention is chemical synthesis of solvates and hydrates, which involves chemical reactions.

e) The state of the art recognizes that the formation, composition and therapeutic activity of solvates and hydrates are unpredictable. The Federal Circuit has recognized a solvate as an example of a polymorph or pseudopolymorph (emphasis added):

> "Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005).

The same rationale obtains for hydrates; solvates in which the solvent is water. Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), recognize that different polymorphs of the same drug can have different therapeutic activity (emphasis added):

> Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity from one form to another may be different. Studying the polymorphism of a drug and the relative stability of the different polymorphs is a critical part of pre-formulation development.

Further, Vippagunta et al. (Advanced Drug Delivery Reviews, 48 (2001), pages 3-26) state "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated in to the crystal lattice of a compound is complex and difficult." See page 18, section 3.4.

f) The artisan using Applicant's disclosure to prepare the claimed solvates and hydrates would be, e.g., an experienced process chemist with at least a BS chemistry degree.

g) Chemical reactions are known as unpredictable. *In re Marzocchi, et al.*, 169 USPQ 367, 370 (CCPA 1971); *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). See above regarding the unpredictability of solvate and hydrate formation.

h) The breadth of the claims includes thousands of compounds of the instant formula (1) as well as presently unknown compounds embraced by the terms solvates and hydrates. See MPEP 2164.01(a), discussed supra, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicant's claimed invention.

Claim Rejections - 35 USC § 103

8. The rejection of claims 1-3, 5 and 12-18 under 35 USC 103(a) over Frigerio et al. (EP 312,867) is maintained.

Applicant argues (a) Frigerio fails to provide any reason explicitly or implicitly that would lead the ordinary artisan in the art to separate the mixture of compounds taught therein, select a specific diastereoisomer and modify it to arrive at the claimed invention, (b) Frigerio does not suggest any superior properties or unexpected results of a single diastereoisomer with respect to the intended purpose or the FXR agonist activity of the compound of the instant application and (c) the Pellicciari declaration filed in application 10/471,549 (now US Patent No. 7,138,390) supports the assertion that structure can not

predict function. Applicant's argument was considered but not persuasive for the following reasons.

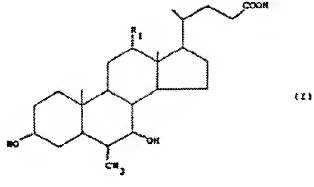
First, the Pellicciari declaration is directed to CDCA/6-methyl CDCA/6-ethyl CDCA and does not provide data directed to UDCA/6-methyl UDCA/6-ethyl UDCA and, thus, does not provide support for the novelty of the claimed invention.

Applicant argues the reference does not explicitly or implicitly provide for the separation of the mixture of compounds taught therein or for the selection of a specific diastereoisomer of the prior art compounds.

The examiner notes that Frigerio states:

> The present invention also relates to the physiologically acceptable salts of compounds of formula I, as well as possible glycine or taurine conjugated forms. Moreover, since compounds I can have the methyl group at 6-position as well as the hydroxy group at 7-position either in α or β configurations, the invention also relates to the single isomers or diastereoisomers and the mixtures thereof.

(see Frigerio page 3, lines 25-28). In essence, the reference is teaching single isomers or diastereoisomers of the compounds of formula I:



(I)

(see Frigerio, page 3, Formula I). Frigerio teaches formula I is inclusive of 6-methyl derivative of ursodeoxycholic (3α,7β OH) and, thus, inherently teaches 6α-methyl- and 6β-UDCA. Frigerio also explicitly teaches 6-methyl UDCA (see page 3, lines 45-46) and, thus, implicitly the use

of either 6α-methyl- or 6β-methyl-UDCA in the treatment of biliary calculosis (see page 3, line 29 - page 4, line 1).

Applicant argues Frigerio does not suggest any superior properties or unexpected results of a single diastereoisomer with respect to the intended purpose or the FXR agonist activity of the instant application. The issue is not whether the reference teaches superior or unexpected properties. The issue is whether the claimed compound would be obvious to the skilled artisan in the art based on the teachings of Frigerio and the level of skill of the ordinary artisan in the art at the time of the present invention.

As noted above, Frigerio explicitly teaches 6-methyl UDCA and implicitly the use of either 6α-methyl- or 6β-methyl-UDCA in the treatment of biliary calculosis. 6-methyl UDCA as taught by Frigerio is the lower adjacent homolog of the claimed compound as stated in the previous Office Actions. The steroid art teaches alkyl substituents differing only in a single $-CH_2-$ would have similar properties (references showing said in the steroid art will be provided upon request). Additionally, the court has held that adjacent homologs are obvious absent a showing of unexpected and obvious results. *In re Henze*, 85 USPQ 261, 263. Applicant has not provided any evidence on record showing the claimed compound has unexpected and/or unobvious properties not possessed by the prior art compound.

For these reasons and those given in the previous Office Action, the rejection of claims 1-3, 5 and 12-18 under 35 USC 103(a) over Frigerio et al. (EP 312,867) is maintained.

Telephone Inquiry

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Barbara P. Badio whose telephone number is 571-272-0609. The examiner can normally be reached on M-F from 6:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Barbara P. Badio/
Primary Examiner, Art Unit 1612